tic meningitis is unusual in patients with systemic lupus erythematosus, recently it has been suggested that aseptic meningitis may be induced by the administration of ibuprofen. We report a case in which aseptic meningitis developed in a patient treated with ibuprofen for systemic lupus erythematosus.

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Clonidine Hydrochloride Withdrawal Complicating Bilateral Nephrectomy

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CLONIDINE HYDROCHLORIDE is an effective antihypertensive agent that has been used in the management of moderate to severe hypertension.[1-5] The presumed site of action is at the level of the brain stem where the drug has a stimulatory effect on a vasomotor inhibitory pathway. Activation of this pathway reduces sympathetic vasomotor tone at the periphery and decreases systemic blood pressure.[6-9] Clonidine hydrochloride has also been shown to decrease the secretion of renin.[10,11]

The abrupt cessation of clonidine administration has been reported to cause a syndrome of sympathetic overactivity (Figure 1). Manifestations associated with this syndrome include severe hypertension, tachycardia, headache, anxiety, nausea, vomiting, and an elevation in serum and urinary catecholamines.[12,14]

Renovascular hypertension has been characterized by some authors as resulting in an elevated renin profile and clonidine has been shown to be effective in lowering the blood pressure of these patients. Strauss and co-workers have suggested that there is a greater risk of the clonidine withdrawal syndrome developing in patients with renovascular hypertension.[15] They suggested that this may be due to simultaneous reactivation of the renin-angiotensin and the catecholamine-sympathetic systems. However, the former has never been documented. We recently encountered a severe episode of hypertension in a patient several hours after bilaterial nephrectomy; the patient had been receiving clonidine for several months before administration was discontinued on the day of surgical operation. This case is presented and a mechanism is proposed for clonidine hydrochloride withdrawal syndrome.

Report of a Case

A 23-year-old white man weighing 60 kg (132 pounds), with chronic renal failure and hypertension secondary to proliferation glomerulonephritis, was admitted to hospital for bilateral nephrectomy in preparation for a kidney transplant.

The preoperative course during the previous six months of dialysis had been complicated by accelerated hypertension; this was unresponsive to salt and water depletion, as manifested by a weight loss of 6 kg. Peripheral vein renin values at this time were 240 ng per ml per hour in the supine position and 245 ng per ml per hour in the upright position (normal 0.5 to 7 ng per ml

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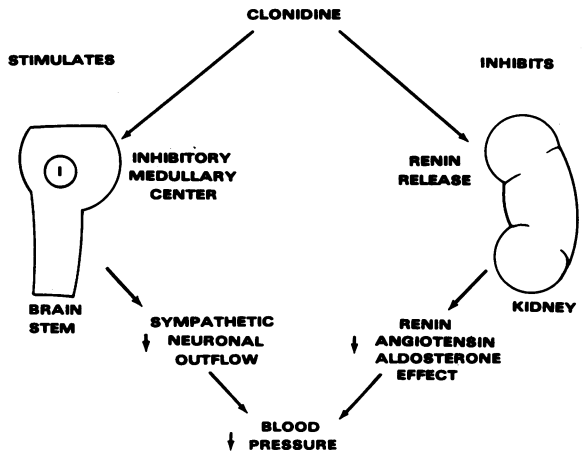

Figure 1.—Clonidine hydrochloride is proposed to stimulate an inhibitory (I) pathway in the medulla by decreasing sympathetic neuronal output and therefore reducing vasomotor tone at the periphery. It also decreases serum renin, and this may lower blood pressure. The sudden cessation of clonidine administration may leave an unopposed excitatory effect on the sympathetic neuronal outflow, which accounts for excess catecholamine levels. Also, it may be related to a rebound increase in renin.

per hour). Urine vanillylmandelic acid and metanephrines, before the onset of advanced renal failure, measured 5.9 and 0.4 mg in 24 hours (normal VMA 1.8 to 8.4 mg in 24 hours; normal metanephrines 0.3 to 0.9 mg in 24 hours). During the course of dialytic therapy the patient's blood pressure remained in the range of 190 to 200 mm of mercury systolic and 110 to 120 mm of mercury diastolic, despite varying doses of clonidine hydrochloride (1.2 to 1.6 mg per day), propranolol (720 to 960 mg per day) and minoxidil (20 to 30 mg per day). Dietary sodium during this interval was 40 mEq per day and interdialytic weight gain averaged 2 kg. One month before the patient's present admission to hospital, mild congestive heart failure developed. Because severe cardiovascular hypertensive disease was uncontrolled by medical therapy, a pretransplantation nephrectomy was scheduled.

Admission was arranged four days before surgical operation to taper the dose of antihypertensive medications. These medications included clonidine hydrochoride, 0.4 mg four times a day; propranolol, 240 mg four times a day; and minoxidil, 10 mg three times a day. The doses of minoxidil and propranolol were reduced 10 mg and 320 mg per day, respectively, and neither was given on the day of the surgical procedure. The dose of clonidine was decreased by 0.4 mg each day and 0.1 mg was given four hours before bilateral nephrectomy. To maintain blood pressure in the range of 160/90 mm of mercury, 500 mg of α-methyldopa was given intravenously every six hours.

Operative findings were limited to bilateral atrophic kidneys. Intraoperative blood pressure remained 120/80 to 130/90 mm of mercury, and there were no complications. Eight hours postoperatively, blood pressure steadily increased from between 150/70 and 160/80 mm of mercury to between 250/100 and 270/120 mm of mercury. This blood pressure rise was associated with a pulse rate of 120 to 140 beats per minute and subjective complaints of pounding in the chest and abdomen. Postoperative weight gain was 1.2 kg and peripheral pulmonary capillary wedge pressure measured 6 to 8 cm of water. Cardiac output ranged from 8 to 9.5 liters per minute, and peripheral resistance was 2,600 dynes per cubic cm.

A nitroprusside infusion, at rates of up to 400 μg per minute, was required to maintain blood pressure in the range of 170/70 to 220/105 mm of mercury. A phentolamine infusion was added on the first postoperative day. Due to limited supply of this agent the rate of infusion never exceeded 0.5 mg per minute. In addition, 0.5 to 1 mg of propranolol was administered intravenously every two hours starting on the second postoperative day to suppress ventricular ectopia and widened pulse pressure which had developed. This combination of agents effectively decreased blood pressure to between 150/60 and 170/80 mm of mercury. Daily dialysis continued during this interval and resulted in a cumulative weight loss of 2.3 kg. At no time were thiocyanate levels in the toxic range.

As a result of a persistent post-operative ileus, oral clonidine therapy was not started again until the seventh postoperative day when 0.4 mg was administered twice a day by mouth. Once clonidine therapy was started again the dose of nitroprusside was decreased and eventually discontinued over the next 24 hours. The remainder of the hospital course was benign and by the 14th postoperative day the patient's blood pressure was 130/70 mm of mercury without administration of antihypertensive medication. Serum catecholamine levels were obtained on the 4th, 8th, and 14th postoperative days; these were 5,338 pg per ml, 713 pg per ml and 213 pg per ml, respectively, (normal 325 to 600 pg per ml).

Peripheral vein renin activity measured on the second postoperative day was undetectable.

Discussion

Severe hypertension developed in the postnephrectomy period, and it was necessary to use potent antihypertensive drugs for several days. The initial blood pressures were significantly higher than those previously observed, either before or during dialytic therapy. Mild hypertension occasionally occurs after nephrectomy and this is thought to be related to hypervolemia, operative stress and pain. Hypertension in this case, however, could not be attributed to hypervolemia because pulmonary capillary wedge pressures were between normal and low. Also adequate analgesia failed to lower blood pressure.

Blood pressure began increasing rapidly 8 to 12 hours after the last dose of clonidine. Of particular significance were the extremely elevated catecholamine levels for the first eight postoperative days. Both these findings are consistent with the clonidine withdrawal syndrome. Epinephrine and norepinephrine are elevated as a metabolic response to surgical operation, but these levels are considerably lower and transient. The possibility of pheochromocytoma was considered remote because of previously normal vanillylmandelic acid and metanephrine urinary screens. Neither propranolol nor minoxidil withdrawal has been associated with a rebound phenomenon.

There probably was an increased risk of clonidine withdrawal syndrome developing in this patient. Hoobler's studies[16] have indicated that this syndrome is more apt to occur when the dose of clonidine exceeds 1.2 mg per day. Strauss and co-workers[15] reported three cases of high renin renovascular hypertension in which severe rebound hypertension developed upon withdrawal of clonidine though 1.0 mg and less per day was administered to the patients. Strauss and co-workers suggested that there may be an increased risk of this syndrome developing in patients with renovascular hypertension, and they proposed a mechanism of renin rebound to account for this phenomenon. Although the peripheral vein renin levels in our patient were elevated preoperatively, postoperative renin activity was undetectable when significant hypertension continued. The extreme level of catecholamines appears to be the sole pressor mechanism responsible for the sustained hypertension. Initially, though, residual renin activity may have served to potentiate hypertension.

The management of clonidine withdrawal has been described.[12,13] Nitroprusside, phentolamine and β-blockers were all successfully used in our case. It would seem that cyanate toxicity was effectively prevented with dialysis. Of note is that reinstitution of oral clonidine therapy reduced blood pressure to normal within 24 hours, and cessation of clonidine therapy three days later did not result in another rebound phenomenon. This suggests that several days or months may be required to establish an environment within the central nervous system that is favorable for rebound phenomena to occur.

The severe and sustained hypertension in this case was attributed to the clonidine withdrawal syndrome, and this is the first report of a case with a postnephrectomy complication. Despite three days of controlled reduction in dosage, rebound hypertension followed complete drug withdrawal. We recommend a considerably longer period of withdrawal preoperatively, as well as catecholamine depletion with reserpine. Fortunately, hypertension, if it occurs, can be managed successfully postoperatively with nitroprusside, phentolamine and propranolol.

Summary

Severe hypertension was encountered in a patient following bilateral nephrectomy for control of renin-mediated hypertensive disease. The rebound hypertension was attributed to clonidine hydrochloride withdrawal and occurred despite gradual preoperative removal of the drug. This is the first reported case of the clonidine withdrawal syndrome complicating bilateral nephrectomy. The anephric state indicates that any contribution by the renin angiotensin system to the development of rebound hypertension is unlikely and implicates excess catecholamines as the sole pressor mechanism. Rapid and prolonged control of blood pressure was obtained through the use of α-blockers or β-blockers, sodium nitroprusside and dialysis.

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Thrombocytopenia Associated With Intravenous Heroin Abuse

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ALTHOUGH multiple medical complications are associated with the intravenous injection of illicit drugs,[1-3] thrombocytopenia has only recently been reported.[4] In only two years we have encountered four cases of intravenous heroin abuse in which patients presented with blood loss due to severe thrombocytopenia. In only one patient was there evidence of concurrent infection. A representative case follows.

Reports of Cases

A 19-year-old man (Case 1, Table 1) was admitted to University Hospital with a ten-day history of easy bruising, blood loss from mucous membranes, melena and hematuria. He had intermittently used heroin intravenously and cocaine for about two years. Results of physical examination showed a temperature of 38.2°C (100.8°F), purpura, petechiae and a palpable spleen tip. Laboratory data included a normal leukocyte count and a platelet count of 1,000 per cu mm. The patient's fever abated in one day without therapy. Administration of prednisone, 100 mg per day, was begun and the platelet count returned to normal levels in ten days. A bone marrow biopsy showed an increase in megakaryocytes and normal cellularity. Prednisone was tapered to 60 mg per day over one week, but thrombocytopenia returned (Figure 1). The patient said he no longer was abusing drugs. Reinstitution of prednisone therapy at 100 mg per day resulted in a return of the platelet count to normal levels in seven days; however, thrombocytopenia recurred during administration of steroids. Splenectomy was done and prednisone again tapered. The platelet count was 276,000 per cu mm when the patient was seen in a follow-up examination 18 months later.

A summary of the clinical characteristics of the four patients we saw is shown in Table 1. As in most cases of drug abuse the patients were young and had used multiple drugs for several years.[1] In case 4 concomitant staphylococcus sepsis was present, but findings on examination for disseminated intravascular coagulation were normal. Although thrombocytopenia may be present in patients with acute bacterial endocarditis, it is an unusual presenting manifestation of this disorder.[5]

In one patient (Case 3) there was a positive radioimmunoassay for hepatitis B antigen but all other liver function tests gave normal findings at the time of presentation. Five weeks later, thrombocytopenia recurred while the patient was on a regimen of 20 mg of prednisone per day. The patient denied intravenous abuse of drugs but admitted to excess intake of alcohol. Findings on

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